New closed-loop system offers promise as novel treatment for post-bariatric hypoglycemia

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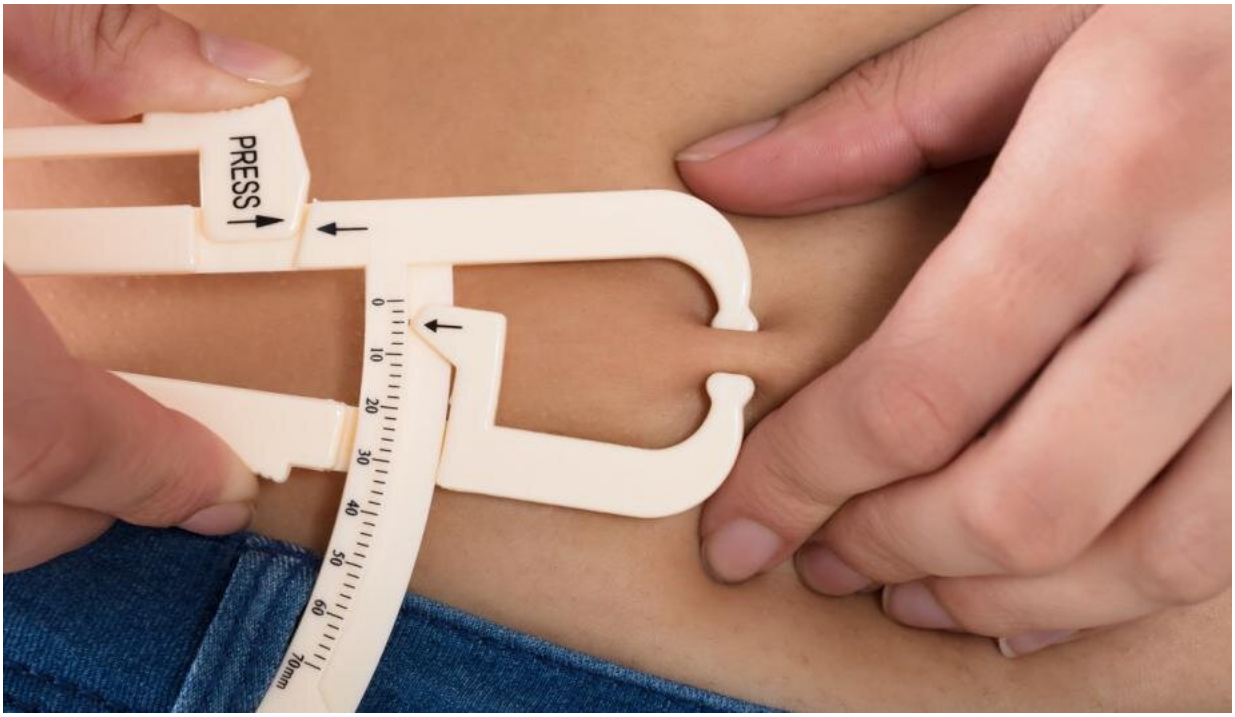

Credit: Andrey Popov

Gastric bypass vastly improves the health of the patients who elect to receive the surgery. Post-bariatric hypoglycemia, however, can be a severe complication experienced by 10 to 30 percent of patients.

Researchers at Joslin Diabetes Center and Harvard John A. Paulson School of Engineering and Applied Sciences have developed a closed-loop system that automatically provides patients with an appropriate, as-needed dose of liquid glucagon to treat this condition. The system, comprised of a continuous glucose monitor (CGM) and a glucagon pump that communicate via an algorithm-controlled application, would allow patients to go about their daily activities without the fear of dipping into dangerous low blood sugar levels. The success of the system was reported on Nov. 13 in *The Journal of Clinical Endocrinology & Metabolism*.

"Post-bariatric hypoglycemia is a profoundly life-altering condition for patients. Having unpredictable hypoglycemia that people can't detect is really an unsafe situation," says Mary Elizabeth Patti, M.D., Associate Professor of Medicine at Harvard Medical School, Investigator at Joslin, and senior author on the paper. "This system provides a way to help individuals keep their glucose in a safe range."

Over two hundred thousand people in the United States have bariatric surgery each year. Some types of these surgeries not only shrink the size of the stomach, but also change the way food travels through the intestines. As a result, high levels of certain hormones are released from the intestine after eating, and these hormones increase insulin production. These changes, in part, account for the reduction in obesity-associated problems, including type 2 diabetes. But in some patients, the surgery can trigger the body to over-produce insulin, leading to sharp drops in blood glucose levels.

"Hypoglycemia can be very disabling," says Dr. Patti. "Since it is not predictable, people can't plan in advance for it. And if it happens repeatedly, people can become unaware that their glucose is low. And if the glucose is severely low, they may have alterations in brain function and may not be able to think clearly. With more severe hypoglycemia,

they may have loss of consciousness and may require the assistance of someone else. It becomes quite a dangerous situation."

Current treatments for post-bariatric hypoglycemia include strictly regulated meal plans, and medications to reduce insulin production after meals. Once a low blood glucose develops, patients have to consume sugar. If the patient has lost consciousness, a family member may have to administer an emergency dose of glucagon, a medication that increases glucose. These treatments, however, are frequently not sufficient on their own and may lead to unhealthy swings in blood sugar.

"This new automated glucagon delivery system is an important development because it helps protect these patients from developing undetected or difficult to treat low blood sugars," says Christopher Mulla, MD, first author on the study. "Glucagon provides patients with a treatment that doesn't involve eating, which they're often afraid of doing, and it does not cause rebound high blood sugars, which can then trigger another low blood sugar."

The system grew from a collaboration between clinical and computational scientists at Joslin Diabetes Center and Harvard John A. Paulson School of Engineering and Applied Sciences. Work on this system began about four years ago, when Dr. Patti realized that artificial pancreas algorithms which had been developed to treat diabetes by study co-senior author Dr. Eyal Dassau, Director, Biomedical Systems Engineering Research Group at the Harvard John A. Paulson School of Engineering and Applied Sciences and his team, could similarly be developed to detect, treat, and prevent severe hypoglycemia.

The team tested whether a glucagon pump and CGM could communicate to provide an adequate dose of glucagon to treat an impending low. During this first phase, glucagon doses were administered by the study physicians. In this newly published paper, the team closed the loop and

allowed Dr. Dassau's algorithm to sense impending low blood sugar levels and automatically deliver an appropriate glucagon dose under supervision by the medical team.

"The way that we look at it, it is very similar to how in your car, you have an airbag," says Dr. Dassau. "You don't use that airbag every time that you stop at a traffic light, but when there is a severe event and there's a need to prevent catastrophe, the airbag will be deployed. We employing the same idea for the glucagon system: we detect, we analyze and then we deliver automatically a mini dose of glucagon."

Twelve patients participated in the study, which took place at Joslin's Clinical Research Center on two separate days. Upon arrival at Joslin, patients were hooked into a CGM and a pump that was filled either with glucagon or a placebo. The study was double-blind, meaning neither the study team nor the patients knew which medication was being delivered which day until the conclusion of the study . The team then induced hypoglycemia in each patient and allowed the algorithm to predict impending or detect current low blood sugar and deliver either glucagon or placebo. The results from each day were analyzed and compared.

"I was very pleased that the system was able to detect hypoglycemia consistently, that the patients were able to tolerate the small dose of glucagon that we used, and that it was effective," says Dr. Patti. "We used about a third of the usual emergency rescue glucagon dose, and that was sufficient to raise the glucose without causing a high glucose level."

Too high a dose of glucagon can lead to vomiting and other symptoms of hyperglycemia, which often occurs in patients given emergency-level doses for hypoglycemia. This new, closed-loop system significantly reduced the risk of over-treating. "That's one of the benefits of automation and running a closed loop. You can start with a very low dose of glucagon as it's needed, and add an additional small dose if indicated

without overdosing," says Dr. Dassau.

The team has already started to adapt the algorithm from a computer application to a cell phone in preparation for the next phase of a clinical trial, which will send the entire system home with study participants to test in a real-world setting.

"We believe that it will provide a particularly helpful therapeutic option," says Dr. Patti. "Using the system to detect an upcoming severe low and treat it before it gets unsafe would be so important to improve safety and quality of life of patients with this type of hypoglycemia."

More information: Christopher M Mulla et al, A Randomized, Placebo-Controlled Double-Blind Trial of a Closed-Loop Glucagon System for Post-Bariatric Hypoglycemia, *The Journal of Clinical Endocrinology & Metabolism* (2019). DOI: 10.1210/clinem/dgz197

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